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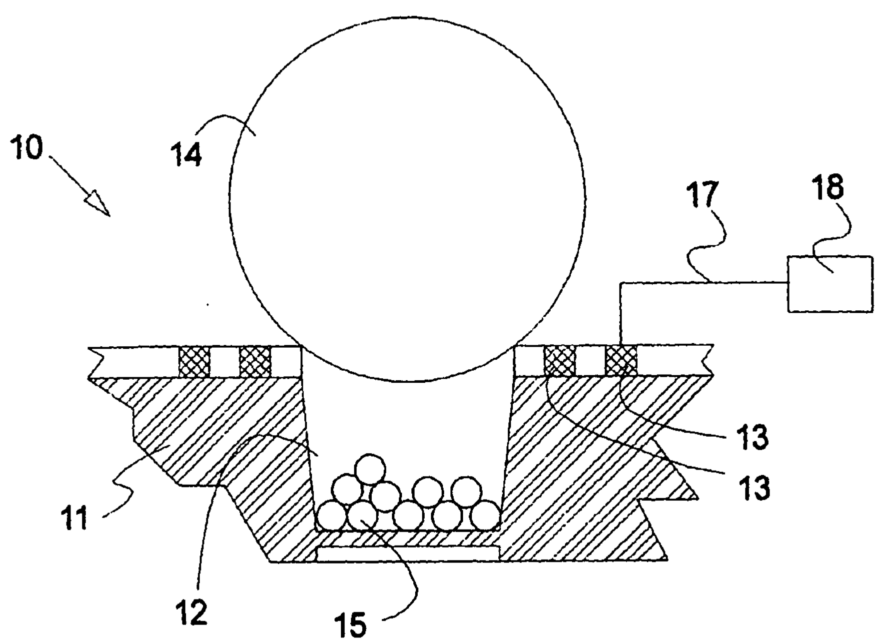
(54) Title: A SAMPLE COLLECTING ARRANGEMENT AND A METHOD



(57) Abstract: The present invention relates to a sample preparing arrangement (10) submergible in a liquid medium, comprising a carrier structure (11), at least one cavity (12) in said carrier, in communication with said cavity an arrangement (13) for controllable generation of a magnetic filed through influence of a control signal. The sample preparing arrangement comprises a magnetic covering structure (4) for covering/uncovering said cavity in operative interaction with said magnetic field.

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A SAMPLE COLLECTING ARRANGEMENT AND A METHOD

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method and arrangement for preparing samples submergible in a liquid medium.

BACKGROUND OF THE INVENTION

Consider a living organism, e.g. a human being or an animal (or even a plant). A basic subunit of such an organism is a cell. One way to catalogize the cells is by the functions they are aimed to perform in an organism, e.g. epithelial cells, (skin) muscle cells, neural cells etc. All these cells communicate with the surrounding world via complex mechanisms, which usually involve many different complex molecules called proteins some of which are embedded into a cell wall. Cells live and die very much like the whole organism; also they grow, divide, etc. In all these functions many different parts/components of a given cell take part. These components can be proteins, enzymes (acting as catalysts for certain reactions occurring in the cell) as well as DNAs, RNAs and tRNAs, etc. Thus there exist an enormous number of processes (mutations) occurring in an organism per unit time and also in each cell of the organism. Some of these mutations are important for the well being, but other are dangerous, like, e.g. cancerous mutations.

Therefore it is very important to be able to foresee, at least partly, the behaviour of a cell, to map out the reactions that occur there and their products (usually creation of new cells DNAs and/or proteins). It is equally important to be able to cure maligneous events in the body, which can arise by either invasion of other organisms (viruses or bacterias) or by processes caused within the body itself (autoimmune reactions), or by outer environmental factors (e.g. stress). In all these processes the number of out coming events is immense. Take for example DNA strands. There are millions and millions of different DNAs, which contribute to production of even larger number of proteins whose function and chemistry is by far more complex then that

of the DNAs themselves.

It would take many lifetimes to establish the structure of even few thousands of the DNA molecules, not to talk about proteins or their functions, or about the drugs. One needs therefore fast techniques enabling acquisition of information in parallel, and effective means of storage and handling of such information.

During the past decades, a search to develop such methods has been started. The common name for such techniques has been coined " high throughput screening" (HTS). The idea is to prepare in parallel as small samples as possible (so as not to use large amounts of expensive and rare chemicals) and as many of these as possible. The easiest and the most logical (from the information handling point of view of) way is to arrange such complex samples in a matrix. Taken from the semiconductor industry these matrices are often referred to as "chips".

One example of such preparation is given in Fig. 1, *Biophotonics, January/February 2000, Univ. of Wisconsin, Franco Cerrina, et al.* According to this technique, a matrix is created by burning away deposits from certain selected places on a chip, while depositing additional chemicals on other places. This method, although fairly fast and cheap, produces a permanent pattern on a matrix, which will be used up after single experiment. Thus, each new experiment requires production of a new matrix.

The number of elements (spots) in a matrix varies depending on the preparation method, but usually does not exceed 10,000, although matrices as large as 1,000,000 sites have been reported. The outcome of each single "experiment" therefore gives at best 10,000 results. In reality this number is much lower (around 20%) due to the very poor quality of even the best matrices produced to date.

FR 2,781,886 concerns fabrication of a microsystem with multiple points for chemical or biological analysis consisting of a structure provided with micro-cups, each micro-cup designed to receive a reagent coupled with a conductor polymer, each micro-cup having a receiving electrode whereon is fixed the reagent via of the polymer conductor, with which it is coupled,

each micro-cup having a counter-electrode arranged so as to apply, in a volume of the micro-cup, an electric field between its counter-electrode and its receiving electrode, the structure having means for simultaneously connecting all the receiving electrodes to a first electric potential and means for simultaneously connecting all the counter-electrodes to a second electric potential for generating said electric field.

US 5,874,219 discloses methods for concurrently processing multiple biological chip assays by providing a biological chip plate comprising a plurality of test wells, each test well having a biological chip having a molecular probe array; introducing samples into the test wells; subjecting the biological chip plate to manipulation by a fluid handling device that automatically performs steps to carry out reactions between target molecules in the samples and probes; and subjecting the biological chip plate to a biological chip plate reader that interrogates the probe arrays to detect any reactions between target molecules and probes.

US 5,755,942 describes a system for processing a plurality of tests or syntheses in parallel comprising a sample channel for moving samples into a micro-laboratory array of a plurality of wells connected by one or more channels for the testing or synthesis of samples, a station for housing the array and an optical system comprising at least one light source and at least one light detector for measuring the samples in the array, and a means of electrically connecting said array to an apparatus capable of monitoring and controlling the flow of fluids into the array. Samples are loaded from a common loading channel into the array, processed in the wells and measurements taken by the optical system. The system uses a magnetic valve for opening and closing a channel for micro-fluids.

SUMMARY OF THE INVENTION

One object of the invention is to present an arrangement which improves the "one by one" experimentation by providing a controllable space.

The technique allows a relatively rapid screening of new chemicals to be used as drugs, both with regard to their function and (importantly) with regard to the determination of the side

effects that a given drug might exert, but can also be used in many other applications such as genome determination, proteomics and others.

The invention can be used to prepare a ready-to-use- product, which is impossible to modify, but to allow a user for possibility to prepare its own "experiment". Thus, one object of the invention is to provide an easy-to-handle platform, which could be used repeatedly and could be prepared in-house. Consequently, the invention is not limited to the surface deposits as is the devices described above (see also fig. 1), but allows sample preparation either by surface deposition (at the bottom or at the walls of a crater) or by utilizing liquid state reactions allowing reagent contained in the liquid trapped within each well by a cap to mix with reagents contained in the liquid above the craters by opening the "lids" (caps) at will.

In the arrangement according to the invention, it is relatively easy to change both the dimensions and the number of the wells. Also the simplicity of the design will allow integrating the reaction product detection system on-chip and perhaps also the facility for multi-well deposition of the active substance.

Another object of the invention is to describe how the detection limits for the events under study can be improved using techniques similar to those used for chip production.

These objects are achieved by the initially mentioned arrangement, which comprises a section provided with a device for controllable generation of a magnetic filed through influence of a control signal, said magnetic field being generated to trap at least part of said samples. Preferably, said device is a coil or a magnetically active material and it is made of an electrically conducting material, preferably aluminium. Each device is applied through a conductor a current of different strength, whereby the current amplitude and the number of windings in the coil are proportional to the strength of the magnetic field.

According to the first aspect of the invention the arrangement comprises a cavity provided in a substrate and a lid for closing said cavity. Preferably, the lid is a magnetic bead. The bead is directed onto a cavity using external magnets that create magnetic fields counteracting the field

created by the material deposited around each cavity. Each cavity is surrounded by a device, which directs said lid using external magnets that creates magnetic fields counteracting the field created by material deposited around each cavity. The cavities are etched in a silicon surface and the lid is provided as a large magnetic particle in the liquid. The particle is attracted to a predetermined cavity when the coil of said cavity is energised by electric current to produce magnetic field of spatial attraction. Before sealing off the cavity, smaller magnetic particles are attracted into the cavity. The sample is a magnetic particle covered with appropriate chemical(s). In one embodiment, the arrangement comprises means for detection of presence of a magnetic capping lid capping a cavity. In one embodiment, the capping is detected by detecting the change in inductance in the control circuit, which produces the attractive magnetic field, whereby the bead acts like a magnetic yoke in a transformer, increasing the inductance. In another embodiment, the capping is detected through decrease of electromagnetic radiation to a detector inside the cavity or by changes of capacitance between electrodes inside the cavity or near a cavity rim.

The arrangement may also comprise means for detection of changes of inductance when a magnetic particle passes through the opening into or out of a cavity. The indication is determined using the direction of externally controlled magnetic field, either by changing the direction of the electric current flowing through a coil or flipping an external magnetic. Preferably, the particle contains particular molecular coating, which reacts with the liquid in that cavity or with the coating adsorbed on the walls of the cavity.

The substrate can be made of silicon, Si, or of Si-compound, such as Si-oxide Si-nitride or Si-carbide, or combinations thereof, or a suitable polymer, such as polyethylene, polyethylene glycol, polyethylene oxide, fluorine containing a polymer (PTFE –Teflon), or silicon containing a polymer.

The invention also relates to a method of preparing samples, by means of an arrangement submergible in a liquid medium, said arrangement comprising a section provided with a device for generation of a magnetic filed. The method comprises the steps of connecting a signal to

said device and generating a magnetic field to trap at least part of said samples. Each device is applied a current of different strength. The arrangement is provided by a cavity in a substrate.

According to the method it is possible to detect presence of a magnetic capping lid capping a cavity. The capping is determined by detecting the change in inductance in the control circuit, which produces the attractive magnetic field, whereby the bead acts like a magnetic yoke in a transformer, increasing the inductance. The capping may also be determined through decrease of electromagnetic radiation to a detector inside the cavity or by changes of capacitance between electrodes inside the cavity or near the cavity rim. According to the method it is possible to detect changes of inductance when a magnetic particle passes through the opening into or out of a cavity, and determining said indication using the direction of externally controlled magnetic field, either by changing the direction of the electric current flowing through a coil or flipping an external magnetic.

According to the method, given a known number of samples in each cavity and a density of respective coatings, quantitative data on the number of reaction between the coating on a wall of the cavity and the coating on a small sample is obtained by counting the number of samples.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following, the invention will be further described in a non-limiting way under reference to the accompanying drawings in which:

Fig. 1 shows an arrangement according to prior art,

Fig. 2 is a schematic view from above of chip according to the invention, and

Fig. 3 is a schematic view, showing an enlarged cross-section along line II-II through a part of the chip according to fig. 2.

DETAILED DESCRIPTION OF THE EMBODIMENTS

The basic idea of the present invention is to create an enclosure or a crater (a well), provided with a lid, which can be opened and closed by a "lid". A user can control the lid and the device is intended to be submerged in a liquid medium. By operating the lid, the enclosed volume

becomes separated from the surroundings. That means, the liquid stored in the crater, particles suspended therein, and/or material that adheres to the craters` inner surface are not affected by subsequent changes that occur in the surroundings while the lid is closed. These changes might be a different chemical composition of the liquid, light shining on the crater chip, or other solids in the surrounding liquid. The lid may or may not be completely liquid-tight, but mixing of the liquid outside a crater with the liquid contained inside a well will be dramatically slowed. Hence, solids and liquids will be well separated between inside and outside, by the lid.

Figs. 2 and 3 illustrate a preferred example of an arrangement according to the invention. Fig. 2 illustratess an enlarged schematic view of a part of chip 19 comprising a number of sample collecting arrangements 10. Each sample collecting arrangement comprises a cavity (crater, pocket, well) 12 provided in a substrate 11 and means 13 to control the cap (lid, cover) 14. Each control means 13 is connected to controller 18 (fig. 3) through connections 17.

Fig. 3 is a schematic cross-section through the device 10. However, the device 10 is shown in a stage where samples 15 are collected and the crater 12 is closed by means of the lid or closure 14. The samples in this particular case are magnetic particles of diameter(s) much smaller than the diameter of the lid, covered with appropriate chemical(s)

In this embodiment, the lid control means 13 comprise electrically actuated coils and the lid 14 is a magnetizeable bead .

By making many craters 12, all with individually controlled lids 14, different types of mixing of solids dispensed in a liquid and/or liquids can be achieved at the same time. As different liquids/solids are introduced to the outside of the craters only user-selected craters with open lids will be reached for the mixing by the liquids/solids external to the closed craters.

The dimensions and the shapes of each crater 12 can of course vary within a large interval both with respect to its diameter and depth. The craters can have circular cross-section, e.g. having about 50 μm deep with the diameters of approximately 100 μm. It is relatively easy to produce

craters with dimensions ranging from few μm and larger and with depth ranging from few μm and up to several hundreds of μm, having, e.g. square shapes.

The material of the substrate can be silicon and the manufacturing process may include micro-machining, similar to the process of making microprocessors or memories chips. A device may contain from several hundreds of craters on a single piece of silicon, providing a so-called chip. Of course tens of thousands of craters on commercial units can be arranged.

Preferably, the lid is a micro-bead introduced in a liquid. The lid-actuation mechanism, i.e. the closing and the opening of each of the craters is performed using switchable magnetic fields that influence the motion of the introduced beads. The magnetic fields are created using the coils 13 deposited around each crater.

The coils 13 surrounding each of the craters are made of an electrically conducting material. In the preferred embodiment the conductor is made of aluminium, Al, but any electrical conductor can be used. Preferably, each coil is accessible through electrically conducting leads so that a current of different strength can be applied separately to each coil. The current amplitude and the number of windings in the coil are proportional to the strength of the magnetic field, which can thus be varied. Clearly, it is possible to change the number of windings in the coils surrounding each crater as well as their width and thickness within a broad range of dimensions. Preferably but not exclusively, coils can have from 2 and up to 10 windings.

In an alternative embodiment, instead of the coils 13, the control means can be substituted by a magnetically active material surrounding each crater and direct the beads using external magnets that will create magnetic fields counteracting the field created by the material deposited around each crater 12.

Preferably, the craters are etched in the silicon surface and the lid is provided by a large magnetic particle 14 in the liquid. Thus, particle 14 can be attracted to the crater of choice when the coil of this crater is energised by electric current to produce magnetic field for spatial attraction. Before sealing off the crater of choice, however, it is also possible to attract smaller

magnetic particles into the crater. To attract the smaller magnetic particles 15 to the crater we energize the coil by leading electric current through it. When the coil is energized, a magnetic field is established. This field will attract the magnetic particle 15 from the liquid. These smaller particles have higher mobility in the liquid compared to the mobility of larger particles and will thus reach crater faster then the larger lids. The large lid-particle will cap the crater at a later stage. Preferably, as large particles commercially available magnetic particles such as ferromagnetic or super-paramagnetic having about 100 micrometers in size can be used, while the size of the smaller particles is much smaller than the crater's size. There are other dimensions and particle types on the market and the invention is applicable a broad range of particle sizes, shapes and materials.

To open a closed crater, a repelling field is generated either externally or by inverting the direction of the current flowing through the coil. It is also possible to terminate the current through the coil, whereby the particle may be released due to shear force from the flowing liquid or due to gravitational forces if the craters are positioned "upside down".

The simple actuation of the crater lid using current controlled magnetic field(s) and the large number of craters on a chip makes it necessary that the chip is operated automatically through controlling arrangement. The chip is preferably provided with an interface device that establishes electrical connection with the chip and provides the handling of the surrounding fluid with the beads and chemicals. After use the chip may be removed for cleaning and reuse or disposal. The interface device will be connected to a computer equipped with suitable software to control the sequence of operations on the craters and the liquid handling system. The software will also provide an interface for the user to establish the process sequence and to plan the states of the crater lids in each sequence.

Detection of a magnetic capping bead can also be done. It is important to obtain feedback on which craters are capped. The presence of a magnetic capping bead, in place over a crater, can be detected by the change in inductance in the electric circuit, which produces the attractive magnetic field. The bead acts like a magnetic yoke in a transformer, increasing the inductance. A resonant, or other, circuit can then detect this inductance change.

The presence of the capping bead can be detected by various other schemes, like the decrease of electromagnetic radiation to a detector inside the crater or by changes of capacitance between electrodes inside the crater or near the crater rim.

Another possible application along similar lines is the detection of changes of inductance when a small magnetic sphere passes through the opening into a well. Using the arrangement according to the invention it is possible to determine whether a sphere is entering the well or if it is leaving the well. This is determined using the direction of externally controlled magnetic field (either by changing the direction of the electric current flowing through a coil or flipping an external magnetic field creating device by other means). Such a sphere may contain particular molecular coating, which will react with the liquid in that well or with the coating adsorbed on the walls of the crater. Given one knows the number of spheres in each well and the density of the respective coatings quantitative data on the number of reaction between the coating on the wall and the coating on a small bead can be obtained by simply counting the spheres.

Following non-limiting examples are given for simplifying the understanding of the invention:

According to a first example liquid A containing magnetic beads is introduced. User selected craters 12 are energized and hence capped. The remaining beads are flushed away with a cleaning liquid. Now liquid B is introduced, containing small (much smaller than the capping beads) particles, called X, made of a material interesting to the user. Only uncapped craters will accept X. Then, more magnetic beads are introduced and selected craters are capped, trapping X. Cleaning liquid will flush all excess away. A liquid containing chemical reagent Y can then be introduced and some craters are opened. X and Y are allowed to mix and react, but only in the user-selected areas. This reaction can be followed using sensing techniques, which can easily be incorporated into the system, for example using optical techniques. Other possible novel detection techniques easily incorporated into the present embodiment are mentioned below.

In a second example, a substance is attached to the craters inner surface. In a repeating sequence some craters are closed by the beads and the others are exposed to a reactive chemical A. After the reaction the chemical is flushed and some craters are exposed to another chemical B. So there will be craters that have been exposed to A and B, some to A, some to B, and some to neither. This process can be repeated with many chemicals producing very large numbers of differently modified substances residing in different locations (craters) of choice. With a sequence of 10 different chemicals, for example, more than 1000 different combinations are obtained. In particular, this could be used to synthesize DNA strands or (using appropriate well-known techniques) to investigate the function(s) of different proteins.

Yet another application is to lock the cells in the wells filled with different chemicals and monitor the reaction of cells (cell proliferation, differentiation, spreading or others) to these chemistries. This would enable, for example a fast high throughput screening of drugs.

The arrangement may also be used separately, one-by-one, for example to deliver a certain chemical or chemicals locally at a certain place or places in a reaction vessel, and monitor reaction products locally, or to deliver a drug inside a body.

Another field of possible applications of the device has been triggered by something generally referred to as a "low throughput screening" (LTS). LTS is often used when the amount of required information is smaller but in addition one wants to obtain some quantitative information about concentrations of analyses or number of reactions that occur during certain time at certain amounts of reagents. The idea behind LTS has much in common with another timely idea often used to day: an "electronic tongue". Electronic tongue is a device that enables one to determine components in a liquid. These components can then be associated with certain tastes (sweet, sour, salt, etc. or combinations thereof). To determine the content of simple liquids in a liquid mixture, for example % of sugar dissolved in a cup of tea along with the amount of tea used to prepare this cup, and even perhaps different tea blends used. To acquire knowledge about all these requires performing several experiments with constituents that react differently to different tea blends and to different amounts of tea from each blend that has been used, as well as to the amounts of sugar being dissolved in this tea. All these can be made by

LTS methods using our equipment and choosing appropriate reagents different for each crater and letting these first to react with a "standard" samples ("learning the tongue" to recognise certain non-mixed liquids) and later exposing these samples to mixtures of different tea blends with or without sugar. Appropriate data processing from the outcome compared with the results obtained on standard samples enables one often to obtain information about tea blends used and the amount of sugar dissolved.

The device is not limited to spheres or coils for creation of magnetic fields that direct beads nor is it limited to the use of beads, and other shapes can be used. Finally it is not limited to the use of silicon technology to fabricate the crater matrices; other materials can be used for this purpose.

Below are additional, non-limiting examples of different crater preparation techniques and materials of use paired with its utilisation:

The general idea behind these examples is to manipulate small particles in order to bring them to a chosen place on the surface of the substrate using magnetic field(s) as a driving force for particle manipulation. The surface of the substrate may be either patterned in a particular manner, or not. When the substrate is patterned and the pattern consists of craters some particles are used preferably as caps or lids to close each crater as described earlier. When the substrate is left without a pattern or patterned in a different manner (see below for an example) the particles can be used mainly as a way to enhance sensitivity of detection of the processes taking place in the device.

The magnetic force to manipulate the particles can be created using coils as described above, but it also may be created using externally applied magnets. In the former case the field strength (and thus the magnitude of the force) is determined primarily by the number of windings in the coil and the magnitude of the electric current. In the latter case it is possible to control the magnitude of the magnetic force by appropriate choice of magnet position and strength.

The substrate may be made of silicon (described above), Si, or of Si-compound, e.g. Si-oxide Si-nitride or Si-carbide, or combinations thereof. It may also consist of thin self-supporting Si,

or of a Si- compound, with another film of suitable thickness (for example few micrometers), such as ZnO, evaporated onto its surface. This additional film is needed if the device is to work as an acoustic wave device for detection.

The substrate may also be fabricated using other material than silicon. For example a suitable polymer, e.g. polyethylene, polyethylene glycol, polyethylene oxide, fluorine containing a polymer (PTFE –Teflon), or silicon containing a polymer, may be used as a substrate material.

When patterning the substrate different techniques may be used depending on the substrate material and the pattern. Thus, Si and Si-compounds are suitably patterned applying well-known techniques from the semiconductor fabrication. When patterning polymers one can use known techniques like polymer stamping or moulding.

It is also possible to supply iron or any other magnetically active material as yoke somewhere inside the crater coil geometry to concentrate the magnetic field to that region, when a coil is activated. This can be inside, below, or around the actual crater. The idea is to build the crater coils in several layers around a crater to increase the magnetic field strength. The crater coils can be used to expel all magnetic material from inside selected craters. Magnetic material can be attracted to the inside of selected craters. Smaller magnetic particles will get attracted to the center of a coil but will sink to the bottom of the crater due to the force of gravity.

It is also possible to in advance prepare the floor or the walls of all the craters as a bio/chem friendly surface, while the rest of the chip surface stays inert, or vice versa. In this way, both the capping beads and the type of surface will determine where a new bio/chem substance will react or be active.

Moreover, capping beads can be used as a chemically/biologically active surface, while the rest of the chip surface is not, or vice versa. By supplying magnetic capping beads, which have been bio/chem prepared in advance, to the chip a particular bead (surface) will be attracted to a pre-determined site. Hence, the user can, by repeatedly applying different beads and washing off unattached beads, cover the chip surface with different and well-defined surfaces. Thus, it is

possible to trigger a chem./bio reaction/activity inside a crater by attracting a capping bead with the right bio/chem active surface.

The invention is not limited the shown embodiments but can be varied in a number of ways without departing from the scope of the appended claims and the arrangement and the method can be implemented in various ways depending on application, functional units, needs and requirements etc.

CLAIMS

1. In a liquid medium submergible sample preparing arrangement (10) comprising a carrier structure (11), at least one cavity (12) in said carrier, in communication with said cavity an arrangement (13) for controllable generation of a magnetic filed through influence of a control signal,
   characterised in
   that said sample preparing arrangement comprises a magnetic covering structure (14) for covering/uncovering said cavity in operative interaction with said magnetic field.

2. The arrangement according to claim 1,
   characterised in
   that said arrangement (13) for controllable generation of a magnetic filed is a coil.

3. The arrangement according to claim 1,
   characterised in
   that a magnetic active material is arranged inside the cavity.

4. The arrangement according to any of preceding claims,
   characterised in
   that the arrangement (13) for controllable generation of a magnetic filed is made of an electrically conducting material, preferably aluminium.

5. The arrangement according to any of preceding claims,
   characterised in
   that said arrangement (13) for controllable generation of a magnetic filed through a conductor (17) is applied a current of different strength.

6. The arrangement according to claim 2,
   characterised in

that a current amplitude and the number of windings in the coil are proportional to the strength of the magnetic field.

7. The arrangement (10) according to any one of claims 1 - 6,
characterised in
that said arrangement comprises a cavity (12) provided in a substrate (11).

8. The arrangement according to claim 7,
characterised in
that it comprises a lid (14) for closing said cavity (12).

9. The arrangement according to claim 8,
characterised in
that said lid (14) is a magnetic bead.

10. The arrangement according to claim 3 and 9,
characterised in
that the bead is directed onto a cavity using external magnets that create magnetic fields counteracting the field created by the material deposited around each cavity (12).

11. The arrangement according to claim 9,
characterised in
that said lid is a micro-bead introduced in said liquid medium.

12. The arrangement according to claim 7,
characterised in
that each cavity is surrounded by a device, which directs said lid using external magnets that creates magnetic fields counteracting the field created by material deposited around each cavity (12).

13. The arrangement according to claim 7,

characterised in

that the cavities are etched in a silicon surface and the lid is provided as a large magnetic particle (14) in the liquid.

14. The arrangement according to claim 13,

characterised in

that said particle (14) is attracted to a predetermined cavity when the coil of said cavity is energised by electric current to produce magnetic field of spatial attraction.

15. The arrangement according to claim 14,

characterised in

that before sealing off the cavity, smaller magnetic particles are attracted into the cavity.

16. The arrangement according to any of preceding claims,

characterised in

that said sample (15) is a magnetic particle covered with appropriate chemical(s).

17. The arrangement according to any of preceding claims,

characterised in

that the arrangement comprises means for detection of presence of a magnetic capping lid capping a cavity.

18. The arrangement according to claim 17,

characterised in

that said capping is detected by detecting the change in inductance in the control circuit, which produces the attractive magnetic field, whereby the bead acts like a magnetic yoke in a transformer, increasing the inductance.

19. The arrangement according to claim 17,

characterised in

that said capping is detected through decrease of electromagnetic radiation to a detector inside the cavity or by changes of capacitance between electrodes inside the cavity or near a cavity rim.

20. The arrangement according to any of preceding claims,
characterised in
that it comprises means for detection of changes of inductance when a magnetic particle passes through the opening into or out of a cavity.

21. The arrangement according to claim 20,
characterised in
that the indication is determined using the direction of externally controlled magnetic field, either by changing the direction of the electric current flowing through a coil or flipping an external magnetic.

22. The arrangement according to claim 20 or 22,
characterised in
that said particle contains particular molecular coating, which reacts with the liquid in that cavity or with the coating adsorbed on the walls of the cavity.

23. 23. The arrangement according to any of claims 7-16,
characterised in
that the substrate is made of silicon, Si, or of Si-compound, such as Si-oxide Si-nitride or Si-carbide, or combinations thereof, or a suitable polymer, such as polyethylene, polyethylene glycol, polyethylene oxide, fluorine containing a polymer (PTFE –Teflon), or silicon containing a polymer.

24. A method of preparing samples (15), by means of an arrangement (10) submergible in a liquid medium, said arrangement comprising a carrier structure (11), at least one cavity (12) in said carrier, in communication with said cavity an arrangement (13) for controllable generation of a magnetic filed through influence of a control signal,

characterised by

25. providing said sample preparing arrangement with a magnetic covering structure (14) for covering/uncovering said cavity in operative interaction with said cavity, and connecting a signal to said device (13) and generating a magnetic field to trap at least part of said samples (15).

26. The method of claim 25,
characterised in
that each device is applied a current of different strength.

27. The method of claim 25,
characterised in
that said arrangement is provided by a cavity (12) in a substrate (11).

28. The method of claim 27,
characterised by
arranging a magnetic lid (14) for closing said cavity (12).

29. The method of claim 28,
characterised by
directing said bead onto a cavity using external magnets that create magnetic fields counteracting the field created by the material deposited around each cavity (12).

30. The method according to any of claims 25-29,
characterised by
attracting smaller magnetic particles into the cavity before sealing off the cavity.

31. The method according to any of claims 25-30,
characterised in
that said sample is a magnetic particle covered with an appropriate chemical(s).

32. The method according to any of claims 25-30, characterised by detection of presence of a magnetic capping lid capping a cavity.

33. The method according to any of preceding claims, characterised by detection of changes of inductance when a magnetic particle passes through the opening into or out of a cavity.

34. The method according to claim 33, characterised by determining said indication using the direction of externally controlled magnetic field, either by changing the direction of the electric current flowing through a coil or flipping an external magnetic.

35. The method according to any of claims 25-34, characterised by given a known number of samples in each cavity and a density of respective coatings, quantitative data on the number of reaction between the coating on a wall of the cavity and the coating on a small sample is obtained by counting the number of samples.

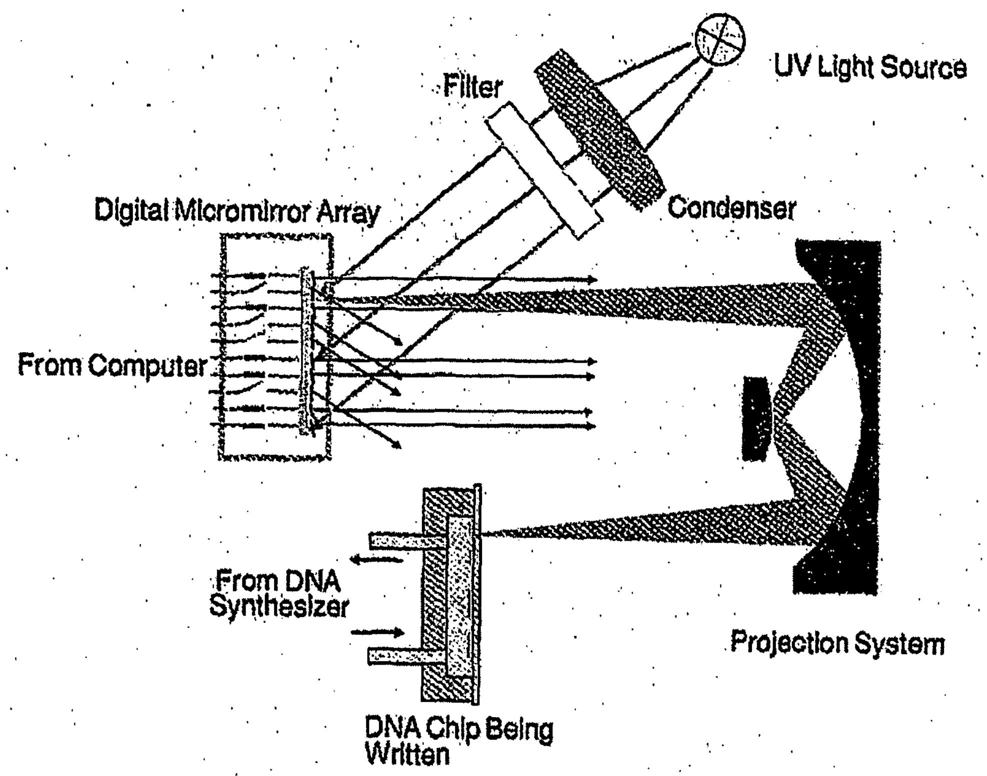
UV Light Source
Filter
Condenser
Digital Micromirror Array
From Computer
From DNA
Synthesizer
Projection System
DNA Chip Being
Written

Fig. 1

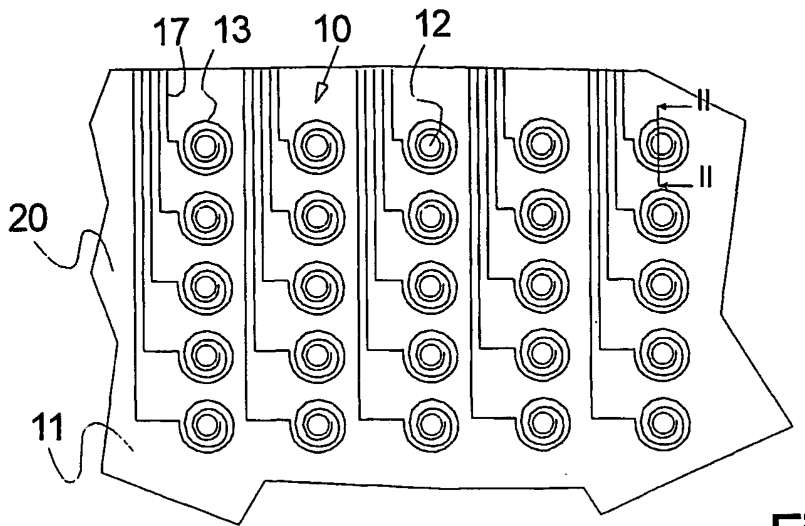

Fig. 2

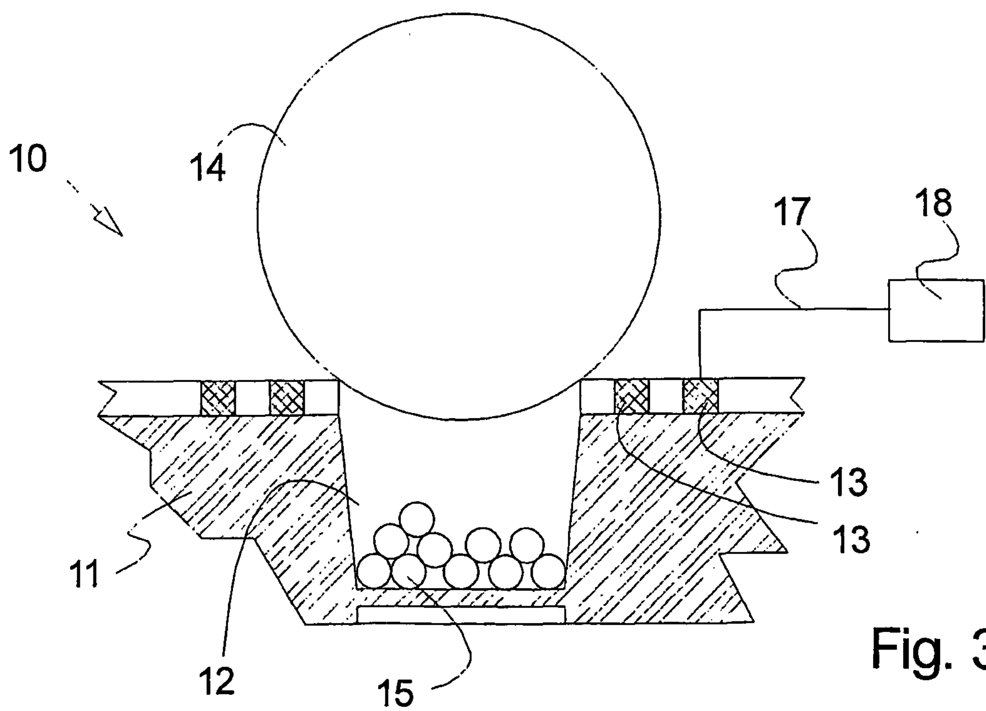

Fig. 3

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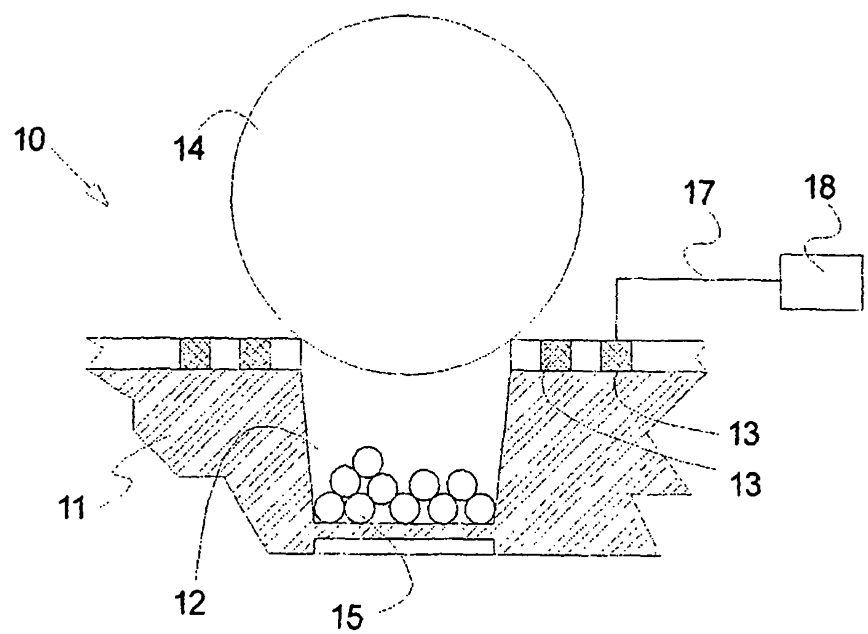
(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European

[Continued on next page]

(54) Title: MICROFLUIDIC DEVICE AND METHOD WITH TRAPPING OF SAMPLE IN CARITIES HAVING LIDS THAT CAN BE OPENED OR CLOSED



(57) Abstract: The present invention relates to a sample preparing arrangement (10) submergible in a liquid medium, comprising a carrier structure (11), at least one cavity (12) in said carrier, in communication with said cavity an arrangement (13) for controllable generation of a magnetic filed through influence of a control signal. The sample preparing arrangement comprises a magnetic covering structure (4) for covering/uncovering said cavity in operative interaction with said magnetic field.

WO 02/16903 A3

patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

(88) Date of publication of the international search report: 30 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01798

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 33/543, C12Q 1/00, B01L 3/00, B03C 1/00, B01J 19/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01N, C12Q, B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO INTERNAL, INSPEC, BIOSIS, WPI DATABASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9615450 A1 (DAVID SARNOFF RESEARCH CENTER, INC.), 23 May 1996 (23.05.96), page 2, line 29 - page 3, line 30, page 10, line 31 - page 11, line 5, page 12, line 36 - page 13, line 11, example 2, figures 6B, 6C and 7C --	1-19,23-31, 35
X	WO 0043534 A1 (SOMALOGIC, INC.), 27 July 2000 (27.07.00), page 14, line 26 - page 15, line 12, page 15, line 24 - page 16, line 3, claim 2 --	1-19,25-31, 35
A	US 5655665 A (MARK G. ALLEN ET AL), 12 August 1997 (12.08.97), columns 1-2, claims --	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2002	27 -02- 2002
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carl-Olof Gustafsson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01798

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0054882 A1 (ARTLOON CORPORATION), 21 Sept 2000 (21.09.00), pages 8-9, pages 42-44, claims, figures 11A, 11B --	1-7,10, 13-16,23
P,X	WO 0060356 A1 (CELLOMICS, INC.), 12 October 2000 (12.10.00), figures 37, 38, page 49, line 21 - page 51 -- --------	1-7,10, 13-16,23-31, 35

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet *

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet **

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

*

The present claims 1- relate to an extremely large number of possible "arrangements" and methods The multitude of alternatives being created by not stating all "means" that are required to obtain the intended function of the arrangement as revealed in the description. In fact, the claim contains so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the whole scope of the claims impossible.
Consequently, the search has been carried out for those parts of the application which appear to be clear and concise, namely *an arrangement and method involving a carrier structure comprising at least one cavity for receiving a sample, a magnetic covering structure (i.e. for magnetic opening/closing the cavity), means (e.g. a coil) for controlled generation of a magnetic field that can open or close the cavity, characterised in that the covering structure is a lid or a magnetic bead.*

**

Invitation to Pay Additional Fees

According to PCT Rules 13.1 and 13.2, an international application shall relate to one invention only or a group of inventions linked by one or more of the same corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art.

In Your application the following inventions have been found:

1. Arrangement and method for "enhancing detection of different samples" comprising a device for "controllable generation of a magnetic field" and further comprising a cavity for receiving the sample and a magnetic covering structure i.e. for magnetic opening/closing operation and means for controlling this activity, characterised in that the covering structure is a lid or a magnetic bead according to claims 1-19 and 23-32 and 37 (partially).

2. Arrangement and method for "enhancing detection of different samples" comprising a device for "controllable generation of a magnetic field" and further comprising a cavity for receiving the sample and a magnetic covering structure i.e. for magnetic opening/closing operation and means for controlling this activity, characterised in that the cavity comprises means for detecting particles entering/leaving the cavity according to claims 20-22 and 33-34 and 35 (partially).

The special technical feature of invention 1 is considered to be the general use of controllable magnetic fields for trapping magnetic particles in a cavity by means of controllable magnetic fields for opening/closing a lid that covers the cavity. The special technical feature of invention 2 is considered to be the use of means for detecting particles entering or leaving a cavity in a method for handling magnetic sample particles.

A new common "special technical feature" does not link invention 1 and 2 required by PCT Art. 13. Arrangements are already known that open or close cavities by means of magnetic fields thereby trapping a sample with a lid in the form of a magnetic particle, e.g. a magnetic ball valve, (see WO9615450 and WO9615576).

Inventions 1 has been searched to the extent it was possible (see the remark for restricted search in Box I).

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/01/02

International application No.
PCT/SE 01/01798

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	9615450	A1	23/05/96	AU	705351	B	20/05/99
				AU	705659	B	27/05/99
				AU	4152396	A	06/06/96
				AU	4233796	A	06/06/96
				CA	2204912	A	23/05/96
				CA	2205066	A	23/05/96
				EP	0791238	A	27/08/97
				EP	0808456	A	26/11/97
				JP	11500602	T	19/01/99
				JP	2001509727	T	24/07/01
				US	5585069	A	17/12/96
				US	5593838	A	14/01/97
				US	5643738	A	01/07/97
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				US	5846396	A	08/12/98
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				US	5863708	A	26/01/99
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US	5655665	A	12/08/97	NONE			
WO	0054882	A1	21/09/00	AU	6045799	A	04/10/00
				CN	1267089	A	20/09/00
WO	0060356	A1	12/10/00	AU	4063700	A	23/10/00
				EP	1166116	A	02/01/02